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(54) **ASSESSING THE RISK OF A MAJOR ADVERSE CARDIAC EVENT IN PATIENTS WITH CHEST PAIN**

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(58) **Field of Classification Search** ..... None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,122,534	A	6/1992	Loose et al.	
5,731,208	A	3/1998	Heinecke	
5,747,274	A	5/1998	Jackowski	
5,871,946	A	2/1999	Lucas et al.	
5,889,042	A	3/1999	MacLean et al.	
5,985,272	A	11/1999	Deby et al.	
6,096,556	A	8/2000	Heinecke	
6,133,039	A	10/2000	Heinecke	
6,268,220	B1	7/2001	Heinecke	
6,953,666	B1	10/2005	Kinkade, Jr. et al.	
7,223,552	B2 *	5/2007	Hazen et al.	435/7.24
2002/0164662	A1	11/2002	Hazen et al.	
2003/0119792	A1	6/2003	Roca	
2003/0180218	A1	9/2003	Hazen	
2006/0051872	A1	3/2006	Sailor et al.	

FOREIGN PATENT DOCUMENTS

EP	0 389 381	9/1990
EP	0 418 486	3/1991
WO	96/04311	2/1996
WO	02/48715	6/2002
WO	02/50550	6/2002
WO	WO 02/062207	8/2002

OTHER PUBLICATIONS

Baldus S et al (published online Sep. 2, 2003) Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. Circulation, vol. 108, pp. 1440-1445.*

Biasucci LM et al (1996) Intracellular neutrophil myeloperoxidase is reduced in unstable angina and acute myocardial infarction, but its reduction is not related to ischemia. J Amer Coll Cardiol, vol. 27, No. 3, pp. 611-616.*

Zhang R et al (Mar. 1, 2002) Defects in leukocyte-mediated initiation of lipid peroxidation in plasma as studied in myeloperoxidase-deficient subjects: systematic identification of multiple endogenous diffusable substrates for myeloperoxidase in plasma. Blood, vol. 99, No. 5, pp. 1802-1810.*

"Association Between Myeloperoxidase Levels and Risk of Coronary Artery Disease" by Zhang, et al., *JAMA*, vol. 286, No. 17, Nov. 7, 2001, pp. 2136-2142.

"Is the Oxidative Modification Hypothesis Relevant to Human Atherosclerosis? Do the Antioxidant Trials Conducted to Date Refute the Hypothesis?" by Steinberg, et al., *Circulation*, 2002; 105:2107-2111.

"Myeloperoxidase Deficiency" by Nauseef, *Hematology, Oncology Clinics of North America*, vol. 2, No. 1, Mar. 1988, pp. 135-158.

"Primary Inherited Defects in Neutrophil Function: Etiology and Treatment" by Malech, et al., *Seminars in Hematology*, vol. 34, No. 4, Oct. 1997, pp. 279-290.

"Mass spectrometric quantification of amino acid oxidation products in proteins: insights into pathways that promote LDL oxidation in the human artery wall" by Heinecke, et al., *FASEB J.*, 13, 1113-1120 (1999).

"Myeloperoxidase-Generated Oxidants and Atherosclerosis" by Podrez, et al., *Free Radical Biology & Medicine*, vol. 28, No. 12, pp. 1717-1725, Jan. 2000.

"Myeloperoxidase, a Catalyst for Lipoprotein Oxidation, Is Expressed in Human Atherosclerosis Lesions" by Daugherty, et al., *J. Clin. Invest.*, vol. 94, Jul. 1994, 437-444.

(Continued)

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(57) **ABSTRACT**

Methods for characterizing the near term risk of experiencing a major adverse cardiac event in a patient presenting with chest pain are provided. In one embodiment the method comprises determining the level of myeloperoxidase (MPO) activity in a bodily sample obtained from the patient. In another embodiment, the method comprises determining the level of MPO mass in a bodily sample obtained from the patient. In another embodiment, the method comprises determining the level of one or more select MPO-generated oxidation products in a bodily sample obtained from the patient. The select MPO-generated oxidation products are dityrosine, nitrotyrosine, chlorotyrosine, methionine sulphoxide or an MPO-generated lipid peroxidation product. Levels of MPO activity, MPO mass, or the select MPO-generated oxidation product in bodily samples from the test subject are then compared to a control value that is derived from measurements of MPO activity, MPO mass, or the select MPO-generated oxidation product in comparable bodily samples obtained from control population. Such comparison can also be used to determine treatment of the patient immediately at presentation in the emergency room.

24 Claims, 2 Drawing Sheets